Patents Office
Government Buildings
Hebron Road
Kilkenny

I HEREBY CERTIFY that annexed hereto is a true copy of documents filed in connection with the following patent application:

Application No.	2000/0304
Date of Filing	13 April 2000
Applicant	PATRICK T. PRENDERGAST, an Irish citizen, of Baybush, Straffan, Co. Kildare.

Dated this 30 day of October 2003.

An officer authorised by the
Controller of Patents, Designs and Trademarks.

2000/0304

FORM NO. 1

REQUEST FOR THE GRANT OF A PATENT

PATENTS ACT, 1992

The Applicant(s) named herein hereby request(s)

[X] the grant of a patent under Part II of the Act

[ ] the grant of a short-term patent under Part III of the Act

on the basis of the information furnished hereunder.

1. Applicant(s)

Name PATRICK T. PRENDERGAST

Address BAYBUSH, STRAFFAN, CO. KILDARE

Description/Nationality

IRISH

2. Title of Invention

1, 2 - dithiole - 3 - thione production

3. Declaration of Priority on basis of previously filed application(s) for same invention (Sections 25 & 26)

Previous filing date	Country in or for which filed	Filing No.

4. Identification of Inventor(s)

Name(s) of person(s) believed by Applicant(s) to be the inventor(s) PATRICK T. PRENDERGAST
DR PAUL ARMSTRONG

Address PATRICK T. PRENDERGAST
BAYBUSH, STRAFFAN, CO. KILDARE
DR PAUL ARMSTRONG
BAYBUSH, STRAFFAN, CO. KILDARE

CONTINUED OVER

5. Statement of right to be granted a patent (Section 17 (2) (b))

6. Items accompanying this Request - tick as appropriate

(i) [X] Prescribed filing fee (£ 100)

(ii) [X] Specification containing a description and claims

[ ] Specification containing a description only

[ ] Drawings referred to in description or claims

(iii) [X] An abstract

(iv) [ ] Copy of previous application(s) whose priority is claimed

(v) [ ] Translation of previous application whose priority is claimed

(vi) [ ] Authorisation of Agent (this may be given at 8 below if this Request is signed by the Applicant(s))

7. Divisional Application(s)

The following information is applicable to the present application which is made under Section 24 -

Earlier Application No: .....
Filing Date: .....

8. Agent

The following is authorised to act as agent in all proceedings connected with the obtaining of a patent to which this request relates and in relation to any patent granted -

Name **Address**

9. Address for Service (if different from that at 8)

PATRICK T. FRENDERGAST
BAYBUSH
STRAFFAN
Co. KILDARE (01-6272636)

Signed Name(s): Patrick T. Frendergast
Capacity (if applicant is a body corporate) :

Date

TITLE: **1,2-DITHIOLE-3-THIONE PRODUCTION**

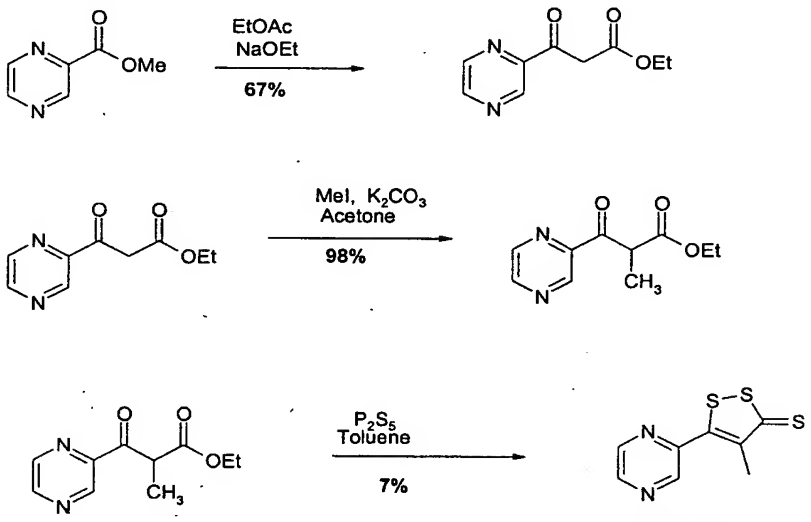
INVENTOR: **Patrick T. Prendergast**
Dr Paul Armstrong

ABSTRACT

The present invention relates to new processes especially suited for the production of a 1,2-dithiole-3-thione drug (Oltipraz).

BACKGROUND OF THE INVENTION

A production process for 1,2-dithiold derivatives has been known in the art. This known process is described in US patent 4,110,450 and is shown below:



Scheme 1

Oltipraz

SUMMARY OF THE INVENTION

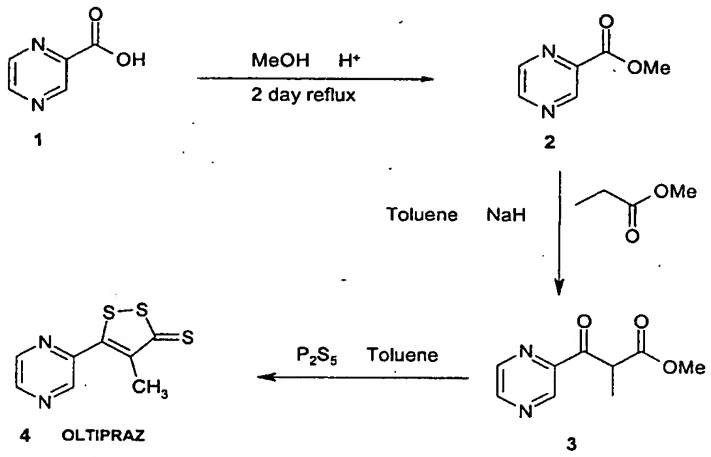
In accordance with a first aspect of the present invention, there is provided a method of synthesising 1,2-dithiole-3-thione comprising the steps outlined below. These steps forming part of one production process are incorporated herein as the inventive embodiment.

The main advantages of this new process compared to previous art are as follows:

1. The preparation of the key intermediate 3 from the pyrazine methyl ester has been reduced to one step by using ethyl propionate rather than ethyl acetate in the condensation step.
2. The starting material in this new route is the much cheaper pyrazine carboxylic acid rather than the ester.
3. In this process intermediates are not isolated so no purification is necessary until the final step. A common solvent, toluene has been successfully used in the final two steps
4. In the final step the workup has been improved by the use of ammonia rather than sodium bicarbonate to neutralise the reaction prior to phase separation. The reaction mixture in the bicarbonate workup proved very difficult to filter.

This process description outlines in detail the process for the preparation of the 1,2-dithiole-3-thione drug Oltipraz in a 3-step pathway and is the current best practical method found. The process is outlined below where each intermediate target **2** and **3** is carried through to the subsequent step as a solution in toluene.

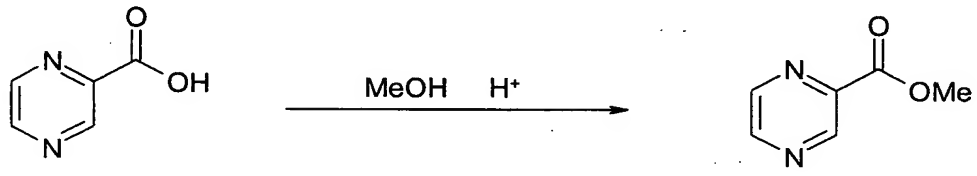
The process route of this patent:



1 2 3 4 OLTIPRAZ

STEP 1 ***Formation of methyl-pyrazine-2-carboxylate 2.***

Pyrazine-2-carboxylic acid **1** undergoes esterification in methanol in the presence of conc. sulfuric acid catalyst[2] to afford the corresponding methyl-pyrazine-2-carboxylate **2** in almost quantitative yield.



1 **2**

$C_5H_4N_2O_2$ $C_6H_6N_2O_2$

M.W. 124.10 M.W. 138.59

Charges:

Reagent & Nature	Supplier	Lot No.	MWt	Wt/g	Vol/ml	mmols
Pyrazine-2-carboxylic acid **1**(99%) Dense solid	Avocado	13363	124.10	50.00	-	402.90
Methanol (99%) Volatile liquid d = 0.791	Aldrich	17,995-7	32.04	-	400.00	-
Conc. Sulfuric acid Non-volatile liquid d = 1.83	Prolabo	20 700.323	98.07	-	0.25	-
Sodium bicarbonate Dense solid	Chemistry stores	GPR	84.00	4.00	-	47.62
GPR Toluene (99%) Volatile liquid d = 0.865	Aldrich	17,996-5	92.14	-	1200.00	-

Theoretical yield = 55.84g
Assumed recovery of 98%.

Procedure:

1.1.1 To a 1L single-neck round-bottomed flask fitted with condenser and drying tube filled with silica gel is charged methanol (400mL) with agitation at room temperature.

1.1.2 Pyrazine-2-carboxylic acid **1** (50.00g, 402.90mmol) is charged to the flask in one portion and the slurry is vigorously stirred.

1.1.3 Conc. sulfuric acid (0.25mL) is charged to the slurry.

1.1.4 The slurry is heated to reflux temperature and stirred at this temperature for 2 days (see note 1.2.1).

1.1.5 The pale yellow solution is allowed to cool to room temperature. This process takes 90 minutes (see note 1.2.2).

1.1.6 Solid sodium bicarbonate (4.00g, 47.62mmol) is added to the solution in one portion and the slurry is stirred vigorously for 30 minutes (see note 1.2.3).

1.1.7 The suspension is filtered (see note 1.2.4).

1.1.8 The filtrate is transferred to a 2L single-neck round-bottomed flask and concentrated to about half volume *in vacuo* @ 35°C (see note 1.2.5).

1.1.9 Toluene (1200mL) is added to the methanol solution and a Dean-Stark trap fitted with drying tube is attached. The solution is heated at atmospheric pressure (external oil bath @120°C) and the first 300mL solvent fraction is run off and discarded (see note 1.2.6).

1.1.10 The Dean-Stark trap is removed and the reaction solution is concentrated in vacuo @45°C to a volume of 300mL (see note 1.2.7).

1.1.11 The organic phase is filtered to remove solid particulates (see note 1.2.8).

1.1.12 The desired methyl-pyrazine-2-carboxylate **2** is then used in the subsequent reaction step as a solution in toluene (see note 1.2.9). A sample is removed and concentrated *in vacuo* @35°C for analysis (refer to Section 1.3).

1.2 Notes

1.2.1 After 4 hours all solid dissolves but TLC analysis (SiO_2) ($CHCl_3$:MeOH) (24:1) still shows the presence of starting acid. TLC analysis after 2 days indicates complete conversion of starting acid.

1.2.2 The pH of the solution at this point is approx. 2.5.

1.2.3 Sodium bicarbonate is added to neutralise the conc. sulfuric acid. Upon addition of solid sodium bicarbonate a granular slurry is observed. After 20 minutes agitation a much finer granular suspension is observed.

1.2.4 A Whatman #1 15cm filter paper is used. The pH of the solution at this point is approx. 7.5.

1.2.5 Approaching half volume concentration methyl-pyrazine-2-carboxylate **2** starts to precipitate from solution but is almost re-solubilised on addition of toluene.

1.2.6 The Dean-Stark apparatus is initially used to remove methanol by gradual substitution with toluene, which is the solvent of choice in Step 2 of the process.

1.2.7 Water generated during esterification is removed azeotropically at this point.

1.2.8 Typically approx. 3.5g of solid is recovered which is a mixture of inorganic salts and **2**.

1.2.9 Water content is determined by Karl Fischer analysis. A typical value of 0.008% is recorded.

1.3 Analysis

Methyl-pyrazine-2-carboxylate (P. A. Goodson, A. R. Oki, J. Glerup and D. J. Hodgson, *J. Am. Chem. Soc.*, **12**, 1190, pp. 6248-6254) isolated as a pale brown solid, m.p. 60-61°C.

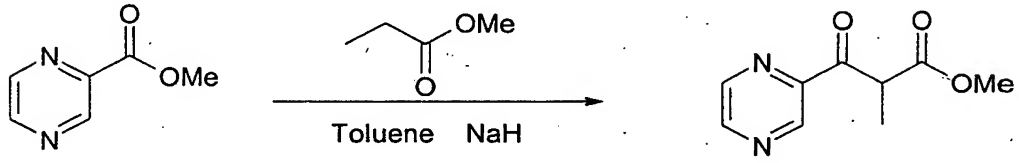
^{1}H NMR analysis of this compound in $CDCl_3$ at 500MHz conforms to structure

^{13}C NMR analysis of this compound in $CDCl_3$ at 125MHz conforms to structure

Karl Fischer water content determined.

STEP 2 ***Formation of methyl-2-methyl-3-(pyrazin-2-yl)-3-oxopropionate 3.***

Methyl-pyrazine-2-carboxylate undergoes a Claisen reaction with methyl propionate using sodium hydride as base to generate the enolate anion. Methyl-2-methyl-3-(pyrazin-2-yl)-3-oxopropionate **3** is produced in high yield.



2 **3**

$C_6H_6N_2O_2$
M.W. 138.59

$C_9H_{10}N_2O_3$
M.W. 194.08

Charges:

Reagent & Nature	Supplier	Lot No.	MWt	Wt/g	Vol/ml	mmols
Methyl-pyrazine-2-carboxylate **2** Dense solid	QuChem	-	138.59	54.72	-	394.83
Methyl propionate (99%) Volatile liquid d = 0.915	Aldrich	10,925-8	88.11	-	53.23	552.77
GPR toluene (99%) Volatile liquid d = 0.865	Aldrich	17,996-5	92.14	-	800.00	-
Sodium hydride (60% dispersion in mineral oil) Dense solid	Aldrich	45,291-2	24.00	22.11	-	552.77
Saturated ammonium chloride soln. Non-volatile liquid	Acros	12334-0010	53.49		500.00	

Theoretical yield = 76.63g
Assumed recovery of 74%.

2.1 Procedure:

2.1.1 To a 2L 3-neck round-bottomed flask under a nitrogen atmosphere is charged NaH (22.11g, 552.77mmol) (60% dispersion in oil).

2.1.2 GPR toluene (250mL) is charged to the flask and the slurry is stirred for 15 minutes at 20°C.

2.1.3 The slurry is allowed to settle. This process takes 45 minutes. Toluene is then removed by decantation (see note 2.2.1).

2.1.4 GPR toluene (250mL) (see note 2.2.2) is charged to the flask and the slurry is stirred at 20°C.

2.1.5 Methyl propionate (53.23mL, 552.77mmol) suspended in anhydrous toluene (250mL) (see note 2.2.3) is added dropwise over 30 minutes (see note 4.4).

2.1.6 The slurry is then heated to reflux temperature (external oil bath @140°C) (see note 2.2.5).

2.1.7 To the refluxing suspension is charged methyl pyrazine-2-carboxylate **2** (54.72g, 394.83mmol) in anhydrous toluene (300mL) (from step 1 of the process) dropwise over a period of 45 minutes (see note 2.2.6).

2.1.8 The reaction contents are heated at reflux temperature for 2.5 hours (see note 2.2.7). The resultant dark brown slurry is allowed to cool to 20°C. This process takes 90 minutes.

2.1.9 Saturated ammonium chloride solution (500mL) is charged to the slurry in one portion. The biphasic solution is vigorously stirred for 120 minutes (see note 2.2.8).

2.1.10 Agitation is stopped after this time and the phases are allowed to settle. This process takes 20 minutes (see note 2.2.9)

2.1.11 The dark brown coloured lower aqueous phase (approx. 500mL) is removed. The yellow/orange coloured upper organic phase (approx. 900mL) is retained.

2.1.12 The aqueous phase is extracted with toluene (2x175mL) and the organic phases are combined (see note 2.2.10).

2.1.13 The organic phase is filtered to remove solid particulates (see note 2.2.11).

2.1.14 The organic phase is concentrated *in vacuo* @45°C to a volume of 400mL (see note 2.2.12).

2.1.15 The desired methyl-2-methyl-3-(pyrazin-2-yl)-3-oxopropionate **3** is then used in the subsequent reaction step as a solution in toluene (see note 2.2.13). A sample is removed and concentrated *in vacuo* @35°C for analysis (refer to Section 2.3).

2.2 Notes

2.2.1 This process is carried out to remove mineral oil.

2.2.2 Water content of GPR toluene is determined by Karl Fischer analysis. A typical value of 0.01% is recorded.

2.2.3 Methyl propionate is only partially miscible with toluene affording a cloudy solution.

2.2.4 Some effervescence is observed due to hydrogen evolution upon enolate formation.

2.2.5 The grey-coloured suspension gradually acquires a pale yellow tinge as the reflux temperature is approached.

2.2.6 Mild effervescence and gas evolution is observed upon addition of methyl pyrazine-2-carboxylate **2** to the enolate anion of methyl propionate. This is an exothermic reaction but the exotherm is controllable with slow addition and at toluene reflux temperature (110°C) where reaction occurs more quickly. No reaction is observed with dropwise addition @70°C.

2.2.7 Reaction progress monitored by TLC analysis (SiO_2 gel) ($CHCl_3$:MeOH) (24:1). Complete consumption of starting material is observed after 2.5 hours at reflux

temperature (110°C) in toluene. During this time the reaction progresses from a yellow colour to a very dark brown coloured slurry.

2.2.8 Methyl-2-methyl-3-(pyrazin-2-yl)-3-oxopropionate **3** is generated as a sodium salt. Saturated ammonium chloride aqueous solution is added to effect conversion to the corresponding protonated species.

Upon addition of saturated ammonium chloride solution the biphasic solution becomes very thick and stirring becomes more difficlut. After several minutes the slurry clears and stirring takes place easily once more.

2.2.9 A small quantity (ca. 3-4g) of solid remains undissolved between the phase interface. This does not affect phase separation and can be removed by filtration through Celite if desired.

2.2.10 Initial phase separation of the quenched reaction mixture affords approx. 55% recovery of the desired methyl-2-methyl-3-(pyrazin-2-yl)-3-oxopropionate **3**. Following one extraction of the separated aqueous phase with toluene increases the recovery of **3** to approx. 75%.

2.2.11 Typically approx. 3g of solid is recovered which is a mixture of inorganic salts and unquenched **3**.

2.2.12 Residual water from the phase separation is removed azeotropically at this point

2.2.13 Water content is determined by Karl Fischer analysis. A typical value of 0.007% is recorded.

2.3 Analysis

Methyl-2-methyl-3-(pyrazin-2-yl)-3-oxopropionate **3** isolated as a viscous oil.

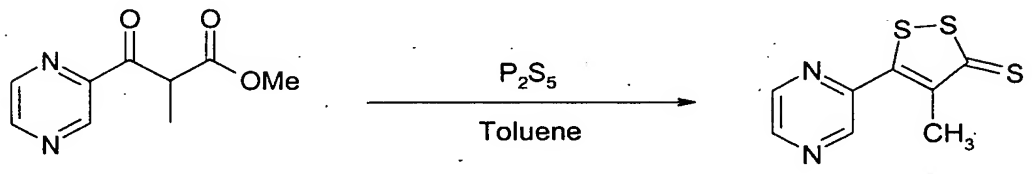
^{1}H NMR analysis of this compound in $CDCl_3$ at 500MHz conforms to structure.

^{13}C NMR analysis of this compound in $CDCl_3$ at 125MHz conforms to structure.

Karl Fischer water content determined.

STEP 3 Formation of Oltipraz 4.

Methyl-2-methyl-3-(pyrazin-2-yl)-3-oxopropionate **3** undergoes thiation and cyclisation with phosphorus pentasulfide to afford Oltipraz **4** as a bright red solid.



3 **4**

$C_9H_{10}N_2O_3$ $C_8H_6N_2S_3$

M.W. 194.08 M.W. 226.24

Charges:

Reagent & Nature	**Supplier**	**Lot No.**	**MWt**	**Wt/g**	**Vol/ml**	**mmols**
Methyl-2-methyl-3-(pyrazin-2-yl)-3-oxopropionate **3** Viscous oil	QuChem	-	194.08	56.70	-	292.15

Phosphorus pentasulfide (98+%) Dense solid	Avocado	17419	222.27	168.83	-	759.58
GPR toluene (99%) Volatile liquid d = 0.865	Aldrich	17,996-5	92.14	-	900.00	-
Conc. ammonia solution 32% Volatile liquid d = 0.88-0.89	Prolabo	21 190.323	17.03	-	270.00	96.54
Methanol (99%) Volatile liquid d = 0.791	Aldrich	17,995-7	32.04	-	140.00	-
Charcoal CG1	Norit	NC 10387	-	1.40	-	-
Acetonitrile (HPLC) Volatile liquid d = 0.781	Acros	26827-0025	41.04	-	450.00	-

Theoretical yield = 66.09g

Isolated yield = 9.73g, 15%.

Recrystallised yield = 6.5g, 10%.

3.1 Procedure:

3.1.1 To a 3L 3-neck round-bottomed flask fitted with pressure-equalising dropping funnel with N_2 inlet, condenser with N_2 outlet and mechanical stirrer and under a nitrogen atmosphere is charged P_2S_5 (168.83g, 759.58mmol) (see note 3.2.1).

3.1.2 GPR toluene (500mL) is charged to the flask and the slurry is stirred at 20°C.

3.1.3 Methyl-2-methyl-3-(pyrazin-2-yl)-3-oxopropionate **3** in GPR toluene (400mL) (from step 2 of the process) is charged to the slurry in one portion.

3.1.4 The yellow slurry is heated to reflux temperature (110°C) (external oil bath @135°C) and stirred at this temperature for 18 hours (see note 3.2.2).

3.1.5 The deep red-coloured slurry is cooled to 0-5°C. This process takes 2 hours.

3.1.6 Water (600mL) is added to the slurry and the thick suspension is brought to pH 8-8.5 by the addition of conc. ammonia solution (270mL) (see note 3.2.3).

3.1.7 The biphasic solution is filtered to remove solid particulates (see note 3.2.4).

3.1.8 The black lower aqueous phase is removed (see note 3.2.5). The deep red-coloured upper organic phase (approx. 1L) is retained.

3.1.9 The aqueous phase is extracted with toluene (2x400mL) and the organic phases are combined.

3.1.10 The organic phase is dried over magnesium sulphate (30g) and concentrated *in vacuo* @45°C to a volume of 100mL (see note 3.2.6).

3.1.11 Methanol (100mL) is added and the slurry obtained is stirred for 20 minutes (see note 3.2.7).

3.1.12 The slurry is filtered through a sintered funnel and washed with methanol (2x20mL).

3.1.13 The dark red solid is dissolved in acetonitrile (approx. 400mL) @78°C and 1.4g of decolourising charcoal is added (see note 3.2.8).

3.1.14 The solution is filtered and cooled to 0-5°C.

3.1.15 The precipitated solid is collected by filtration through a sintered funnel and washed with ice cold acetonitrile (1x40mL) to afford Oltipraz **4** as bright red needles (approx. 6.5g, 10%).

3.2 Notes:

3.2.1 A range of molar equivalents of phosphorus pentasulfide (from 1.5 to 4) was used with little or no variation to the isolated yield of Oltipraz.

3.2.2 Reaction progress monitored by TLC analysis (SiO_2 gel) ($CHCl_3$:MeOH) (24:1). Almost complete consumption of starting material is observed after 18 hours at reflux temperature (110°C) in toluene. During this time the reaction progresses from a yellow colour to a dark red coloured slurry.

3.2.3 Addition of conc. ammonia solution results in a slight exotherm and the internal flask temperature rises to 32°C. As the pH of the suspension approaches 8 the solid slurry almost clears completely and two separate phases are obtained.

3.2.4 The biphasic solution is filtered through Celite (sinter, porosity #3).

3.2.5 A volume of 800mL of aqueous layer is removed.

3.2.6 At this point Oltipraz precipitates from the toluene solution.

3.2.7 Addition of methanol aids the precipitation of Oltipraz.

3.2.8 Recrystallisation in the presence of charcoal.

3.3 Analysis

Oltipraz **4** isolated as a bright red solid, m.p. 167-168°C.

^{1}H NMR analysis of this compound in $CDCl_3$ at 500MHz conforms to structure

HPLC analysis of this compound

^{1}H NMR analysis of Oltipraz standard (3 x recrystallisations in acetonitrile) in $CDCl_3$ at 500MHz conforms to structure

HPLC analyses of Oltipraz standard

Karl Fischer water content and HPLC analyses

This description forms the embodiment of this invention.